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Clinical article

Constantin Tuleasca, M.D.,[1,4–7] Romain Carron, M.D., Ph.D.,[1] Noémie Resseguier, M.D., M.Sc.,[2] Anne Donnet, M.D.,[3] Philippe Roussel, M.D.,[1] Jean Gaudart, M.D., Ph.D.,[2] Marc Levivier, M.D., Ph.D.,[6,7] and Jean Régis, M.D.[1]

[1]INSERM U 751 (Université de la Méditerranée), Functional and Stereotactic Neurosurgery Unit; [2]Department of Public Health and Medical Information and UMR 912 (INSERM-IRD–Université de la Méditerranée); and [3]Department of Neurology, Clinical Neuroscience Federation, Centre Hospitalier Universitaire La Timone Assistance Publique–Hôpitaux de Marseille, France; [4]Signal Processing Laboratory (LTS 5), École polytechnique fédérale de Lausanne; [5]Medical Image Analysis Laboratory; [6]Department of Clinical Neurosciences, Neurosurgery Service and Gamma Knife Center, Centre Hospitalier Universitaire Vaudois; and [7]Faculty of Biology and Medicine, University of Lausanne, Switzerland

Object. The purpose of this study was to establish the safety and efficacy of repeat Gamma Knife surgery (GKS) for recurrent trigeminal neuralgia (TN).

Methods. Using the prospective database of TN patients treated with GKS in Timone University Hospital (Marseille, France), data were analyzed for 737 patients undergoing GKS for TN Type 1 from July 1992 to November 2010. Among the 497 patients with initial pain cessation, 34.4% (157/456 with ≥ 1-year follow-up) experienced at least 1 recurrence. Thirteen patients (1.8%) were considered for a second GKS, proposed only if the patients had good and prolonged initial pain cessation after the first GKS, with no other treatment alternative at the moment of recurrence. As for the first GKS, a single 4-mm isocenter was positioned in the cisternal portion of the trigeminal nerve at a median distance of 7.6 mm (range 4–14 mm) anterior to the emergence of the nerve (retrogasserian target). A median maximum dose of 90 Gy (range 70–90 Gy) was delivered. Data for 9 patients with at least 1-year follow-up were analyzed. A systematic review of literature was also performed, and results are compared with those of the Marseille study.

Results. The median time to retreatment in the Marseille study was 72 months (range 12–125 months) and in the literature it was 17 months (range 3–146 months). In the Marseille study, the median follow-up period was 33.9 months (range 12–96 months), and 8 of 9 patients (88.9%) had initial pain cessation with a median of 6.5 days (range 1–180 days). The actuarial rate for new hypesthesia was 33.3% at 6 months and 50% at 1 year, which remained stable for 7 years. The actuarial probabilities of maintaining pain relief without medication at 6 months and 1 year were 100% and 75%, respectively, and remained stable for 7 years. The systematic review analyzed 20 peer-reviewed studies reporting outcomes for repeat GKS for recurrent TN, with a total of 626 patients. Both the selection of the cases for retreatment and the way of reporting outcomes vary widely among studies, with a median rate for initial pain cessation of 88% (range 60%–100%) and for new hypesthesia of 33% (range 11%–80%).

Conclusions. Results from the Marseille study raise the question of surgical alternatives after failed GKS for TN. The rates of initial pain cessation and recurrence seem comparable to, or even better than, those of the first GKS, according to different studies, but toxicity is much higher, both in the Marseille study and in the published data. Neither the Marseille study data nor literature data answer the 3 cardinal questions regarding repeat radiosurgery in recurrent TN: which patients to retreat, which target is optimal, and which dose to use.
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Key Words • Gamma Knife surgery • trigeminal neuralgia • retreatment • stereotactic radiosurgery

Gamma Knife surgery (GKS) is a noninvasive procedure, increasingly used in many intracranial conditions, including trigeminal neuralgia (TN). Leksell, the inventor of GKS, performed the first radiosurgical treatment in 1951.[35,36] In 1981, Håkanson discovered that the glycerol injection, made for GKS targeting purposes, could also be used as a therapy in TN.[20,21] In 1985, once MR imaging was available for clinical use on a large scale, modern dose planning was implemented.[37] In 1993, Rand et al.[45,46] advocated that the ganglion was not a good target and proposed to shift the target to the

Abbreviations used in this paper: BNI = Barrow Neurological Institute; DREZ = dorsal root entry zone; GKS = Gamma Knife surgery; MVD = microvascular decompression; TN = trigeminal neuralgia.

cisternal part.[50] In 1996, Kondziolka et al.[34] published a multicenter study that established the minimal therapeutic dose necessary to be effective.[50] In 1994, Lindquist coined the term "dorsal root entry zone (DREZ) target" (corresponding in fact to the anatomical emergence of the trigeminal nerve).[37] In 2000, Pollock et al.[43] published the first paper on repeat radiosurgery for TN, and in 2006 Régis et al.[49] published the only prospective controlled trial using GKS as a therapy for medically unresponsive TN.

Since 1996, the number of available papers advocating the safety and efficacy of GKS in idiopathic TN has grown continuously; however, studies describing repeat radiosurgery are scarce. Furthermore, there are no clear-cut guidelines for indication or technique for repeat radiosurgery, such as patient selection criteria for retreatment, dose, location of the isocenter, or whether to plug the collimator apertures. Therefore, we present our own study of patients treated in Timone University Hospital, Marseille, France, and compare our results with systematically reviewed published data on repeat radiosurgery for recurrent TN.

Methods

Marseille Study

This was designed as an open, self-controlled, noncomparative, retrospective study. For all patients, a case report form was created and filled in prospectively. All patients were examined before treatment, and MR imaging was performed (the latest images were used to exclude any secondary cases). Permission was obtained from the Timone University Hospital ethics committee for this study.

Patients. Between July 1992 and November 2010, patients presenting with intractable TN were prospectively selected and treated with radiosurgery in Timone University Hospital, Marseille, France. We included in our study patients undergoing repeat GKS for recurrent TN with more than 1 year of follow-up.

Cases of TN secondary to multiple sclerosis[58] or due to megadolichobasilar artery compression[60] were excluded from our analysis, as they are reputed to have different clinical outcomes.

All patients were treated by the senior neurosurgeon (J.R.).

Diagnostic Criteria Using the International Headache Society Definition. All patients fulfilled the TN criteria of the International Headache Society.[23] Evaluation of the type of trigeminal pain was made according to the classification proposed by Eller et al.[15]: idiopathic TN Type 1, described as typically sharp, shooting, electrical shock–like, with pain-free intervals between the attacks, present for more than 50% of the time; and TN Type 2, described as an aching, throbbing, or burning pain, present for more than 50% of the time and constant in nature (constant background pain being the most significant attribute). Only patients fulfilling the criteria of the TN Type 1 were included in the present study.

Patient Selection Criteria for Retreatment and Technique. Retreatment was proposed only if patients had good and prolonged pain cessation after initial GKS, with no other surgical alternative at the moment of recurrence. We used the same target and same ranges of doses as for the first GKS. All patients underwent repeat GKS. After application of the Leksell Model G stereotactic frame (Elekta AB) under local anesthesia, patients underwent stereotactic MR imaging and CT imaging for target definition. The MR image sequences used to identify the trigeminal nerve were T2-type CISS (constructive interference in steady state) (Siemens S.A.S.) without contrast, and contrast-enhanced T1-weighted images. Bone CT imaging routinely supplements the neuroradiological investigation to correct any distortion errors on the MR image.[49,59]

Between July 1992 and November 2010, the Gamma Knife (model B, C, or 4C; Elekta AB) was successively used. A single 4-mm isocenter was used in all patients, for both the first and the second GKS, positioned in the anterior cisternal portion of the trigeminal nerve at a median distance of 7.6 mm (range 4–14 mm) anterior to the emergence of the nerve (retrogasserian target). This target has been used in our center since the beginning of GKS treatments for TN, as detailed in previous studies[47–50] (Fig. 1).

The median maximum dose delivered during the first treatment was 85 Gy (range 70–90 Gy) and at retreatment it was 90 Gy (range 70–90 Gy). The dose was chosen according to the multicenter trial of Kondziolka et al.[34] (which included an substantial number of patients from our center), which recommended a minimal dose of 70 Gy for short- and/or long-term efficacy, a cutoff our group was using before the publication of that trial. Furthermore, we initially give a dose of 90 Gy at the 100% isodose. Beam channel blocking is used based on the dose received by 10 mm^3 of the brainstem: if this dose is greater than 15 Gy, we diminish the dose and then start plugging the collimator apertures to avoid increasing the length of the treated nerve, which could account for more toxicity (the so-called Flickinger effect).[16]

Follow-Up Monitoring. Patients and referring physicians were instructed to follow the pretreatment medication regimen for at least 1 month after GKS and then to diminish the doses progressively in periods of pain freedom.

Initial follow-up was based on clinical evaluation at regular intervals of 3 months, 6 months, and 1 year after the treatment and on a yearly basis thereafter. We have personally examined all patients for proper evaluation of safety and efficacy, including facial sensory testing, corneal reflex, and jaw motility. For long-term follow-up, telephone interview was considered acceptable for patients unable to visit the clinic because of either distance or general health-related conditions.

Every clinical evaluation made by our medical team during follow-up was prospectively noted in the database. The 15 items of data considered essential by Zakrzewska and Thomas[66] for articles reporting outcomes of surgical treatment of TN were followed.

Explicit Definitions of Outcome Measures. Outcome measures included initial pain cessation and onset and recurrence of the sensory disturbance. Efficacy was classi-

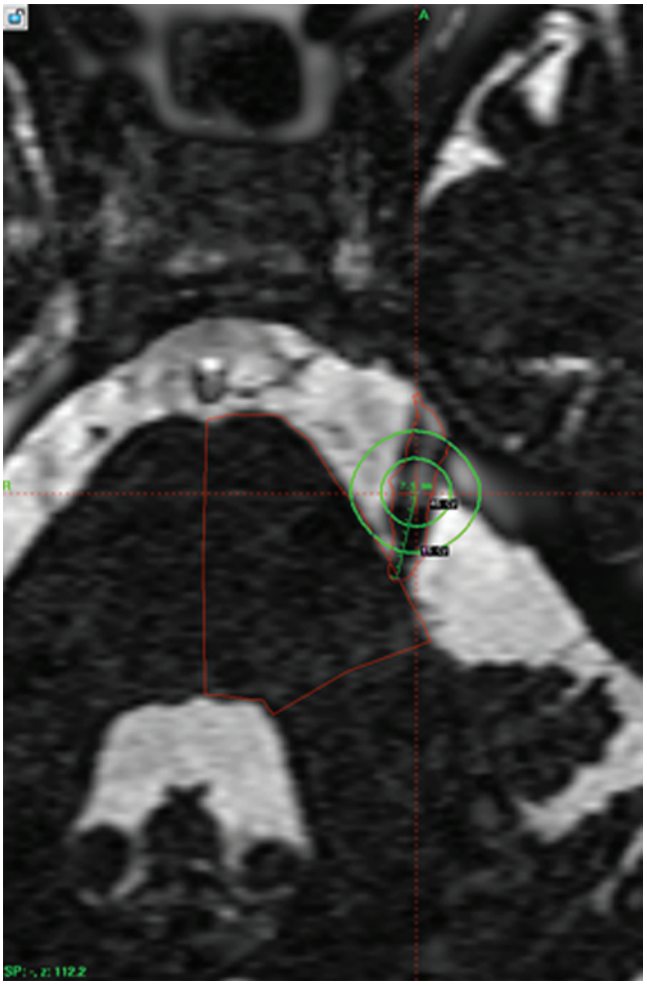

Fig. 1. The retrogasserian target used in our institution (Timone University Hospital, Marseille, France).

fied according to the Barrow Neurological Institute (BNI) scale: Class I, no trigeminal pain, no medication; Class II, occasional pain, not requiring medication; Class IIIa, no pain with continued medication; Class IIIb, pain controlled with medication; Class IV, some pain, not adequately controlled with medication; and Class V, severe pain, no pain relief. A successfully treated patient was considered a patient who was pain free without medication (BNI Class I).

The degree of hypesthesia is reported using the BNI facial hypesthesia scale: Class I, no facial numbness; Class II, mild facial numbness, not bothersome; Class III, facial numbness, somewhat bothersome; and Class IV, facial numbness, very bothersome.[51] The corneal reflex was assessed for all patients. Additionally, the occurrence or absence of dysesthesias, paresthesias, anesthesia dolorosa, masseter weakness, neurological complications outside the trigeminal nerve territory, systemic complications, and death were noted.

Recurrence was defined as change from Class I to a lower outcome class during follow-up. Thus, recurrence was considered to have happened in a patient who had been pain free without medication (Class I) and who then started taking specific drugs again but who remained pain free on medication (Class II).

A minor recurrence was defined as one that was well tolerated by the patient (lower frequency and intensity of the pain) and did not require additional treatment. A major recurrence was defined as one requiring a surgical procedure. We use the term "initial efficacy" when a patient is pain free with or without medication in the first 6 months after the radiosurgery and has no recurrence in the year that follows the procedure.

The latency intervals to becoming pain free or developing a recurrence or a sensory disturbance, the date of medication changes, and the date of all surgical procedures were also monitored. Patient satisfaction was evaluated at the last follow-up.

Statistical Analysis. All statistical analyses were performed using R software (version 2.12.0, R Foundation for Statistical Computing). The R package "survival" was used for survival analysis. For the evaluation of outcomes such as pain free, hypesthesia, and recurrence, time to event was estimated using the Kaplan-Meier method. A bivariate analysis was then performed to identify predictive factors among the collected variables. Qualitative variables were compared using the univariate log-rank test, with survival among the different groups represented graphically with Kaplan-Meier curves. For all variables, the effects were estimated and tested by fitting univariate Cox proportional hazards regression models. Proportionality of hazards was assessed graphically by log cumulative hazard plots. For qualitative variables, chi-square tests were performed when valid; otherwise, exact Fisher tests were used. For quantitative variables, Mann-Whitney tests were performed given the number of patients. All tests were 2-sided, and p values < 0.05 were deemed significant.

Systematic Review

Search Strategy and Selection Criteria. The PubMed database was queried using the following word combinations in the "title" item: ("repeat" AND "radiosurgery" AND "trigeminal"), ("recurrent" AND "radiosurgery" AND "trigeminal"), and ("salvage" AND "radiosurgery" AND "trigeminal"). The bibliographies of the identified studies were also searched to ensure that no qualifying references were missed. Additionally, we used the Google search engine to expand our list of studies, including abstracts, but we considered in the final analysis only peer-reviewed papers. We did not restrict returns by year of publication; all published studies were eligible for selection if they fulfilled the criteria. There were no language restrictions.

Suitable studies were peer reviewed and contained data on patients who underwent repeat radiosurgery for recurrent TN, and reported rates of initial pain cessation, hypesthesia, and recurrence. Papers reporting retreatment as a subgroup were included if they had a minimum number of 13 cases, as this was the number of our study. We excluded studies that did not meet these criteria.

Three investigators (C.T., M.L., and J.R.) extracted data independently and in duplicate and assessed trial eligibility and quality. Disagreements were resolved by consensus.

Outcomes. We extracted the primary outcomes, initial pain cessation, hypesthesia, and recurrence, and their positive and negative predictive factors. Secondary data extracted were selection criteria and patient profile for retreatment, the number of retreatments versus the total number of patients in the same institution/trial, mean/median interval between first and second radiosurgical treatments, placement of the target and the doses used for first and second treatments, complications other than hypesthesia, and criteria used to report the outcomes.

Results

Marseille Study

Between July 1992 and November 2010, 737 patients were treated for TN at Timone University Hospital (Marseille, France). Among the 497 patients in our study with initial pain cessation after the first GKS, 34.4% (157 of 456 patients with ≥ 1-year follow-up) experienced at least 1 recurrence. Thirteen of the 737 patients (1.8%) had repeat GKS for recurrent TN; 9 patients with more than 1 year of follow-up were further analyzed. The median follow-up period for these 9 patients was 33.9 months (range 12–96 months). The median age at second GKS was 64.4 years (range 53.7–83.1 years). All the patients presented with typical TN Type 1 pain.

Details of Previous Treatments. Previous treatments are detailed in Table 1. All patients (100%) had prior surgical procedures, of whom 4 (44.4%) had only 1 previous intervention, 2 (22.2%) had 2 previous surgeries, and 3 (33.4%) had 3 or more previous surgeries. Previous surgeries consisted of radiofrequency lesioning in 4 patients (44.4%), balloon microcompression in 1 (11.1%), and microvascular decompression (MVD) in 1 (11.1%). Before GKS, 3 patients (33.3%) had sensory disturbance related to a previous surgical procedure, consisting of slight hypesthesia in 2 (22.2%) and severe hypesthesia in 1 (11.1%).

Initial Rate of Pain Cessation. Eight of 9 patients (88.9%) were initially pain free in a median time of 6.5 days (range 1–180 days) after retreatment and 10 days (range 1–180 days) after first GKS. The initially pain cessation actuarial rate at 0.5, 1, 2, 3, 4, 5, and 6 months was, respectively, 53.52%, 73%, 83.5%, 88.1%, 88.9%, 89.5%, and 91.3% after the first GKS (Fig. 2) and 33.3%, 44.4%, 44.4%, 55.6%, 55.6%, 66.7%, and 88.9% after retreatment. No statistically significant predictors were found for being initially pain free after the second GKS, but the small number of patients limits statistical power.

Postoperative Sensory Assessment. No patients sustained early complication after the second GKS. Three patients (33.3%) developed later objective facial sensory loss, which occurred during the 1st year after retreatment and was mild in all cases. The hypesthesia actuarial rate was 33.3% at 6 months; at 1 year it reached 50% and remained stable for 7 years (Fig. 3). For all patients with idiopathic TN treated in our institution, we have reported a hypesthesia actuarial rate of 21% after first GKS;[48] in our study of patients undergoing repeat radiosurgery, we found a statistically significant higher risk of facial numbness ($p = 0.0193$; hazard ratio 3.97). We also assessed hypesthesia according to the BNI facial hypesthesia scale; mild facial numbness occurred in all 3 patients. No patient developed a trigeminal motor deficit or other cranial nerve deficit, or anesthesia dolorosa or dry eye syndrome after GKS. When asked about their quality of life, all patients considered the presence of hypesthesia to be a good tradeoff for the disappearance of pain. No statistically significant predictors were found for complications after the second GKS, but the small number of patients limits statistical power.

TABLE 1: Pretreatment assessment in the Marseille study (n = 9)

Variable	No. of Patients (%)
side of pain	
right	6 (66.7)
left	3 (33.3)
no. of prior treatments	9 (100)
1	4 (44.4)
2	2 (22.2)
≥3	3 (33.4)
type of prior treatment	
GKS	9 (100)
radiofrequency lesioning	4 (44.4)
balloon microcompression	1 (11.1)
MVD	1 (11.1)
side effects from prior surgery	3 (33.3)
facial sensation before GKS	
normal	6 (60.5)
slight hypesthesia	2 (22.2)
severe hypesthesia	1 (11.1)

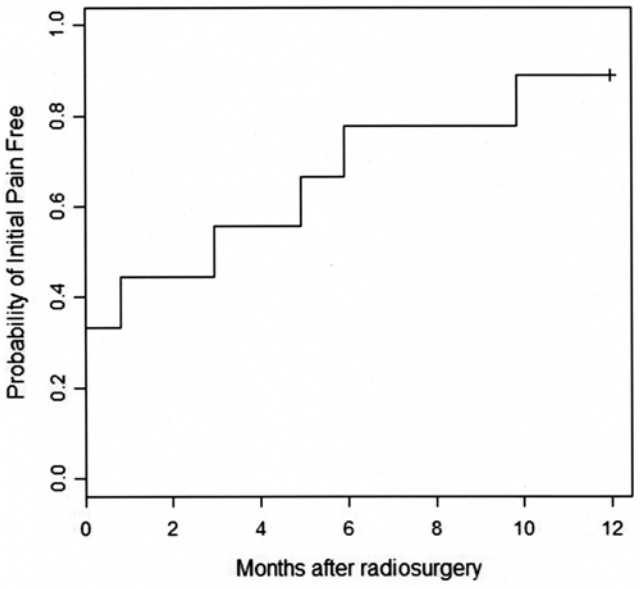

Fig. 2. Kaplan-Meier curve showing the actuarial pain cessation rates in our series after second GKS (9 patients with ≥ 1-year follow-up).

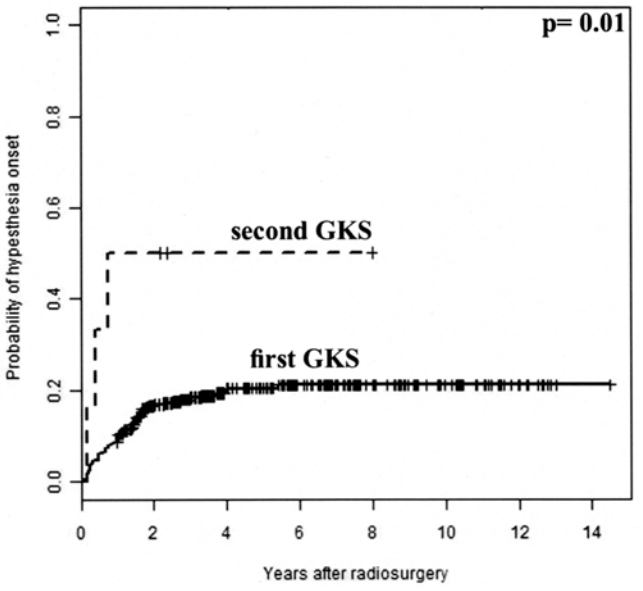

Fig. 3. Kaplan-Meier curve showing the actuarial hypesthesia rates for first GKS *(solid line)* and second GKS *(dashed line)*.

Management and Results of Recurrent Pain. Two patients (22.2%) who were initially pain free after GKS experienced a recurrence. The actuarial probability of maintaining pain relief without medication at 6 months was 100% and at 1 year reached 75% and remained stable for 7 years (Fig. 4). Patients with pain on the left side ($p = 0.04$) and in the V2 dermatome ($p = 0.04$) had a higher risk of recurrence. No other statistically significant predictors were found, but the small number of patients limits its statistical power.

Two patients (22.2%) needed an additional treatment after GKS, with 1 surgery in 1 case (11.1%) and 3 or more surgeries in 1 case (11.1%). The further surgical procedures performed were balloon microcompression in 2 cases (22.2%) and MVD in 1 case (11.1%) (Table 2). All patients (100%) expressed a high level of satisfaction, did not regret undergoing GKS, and would undergo GKS again.

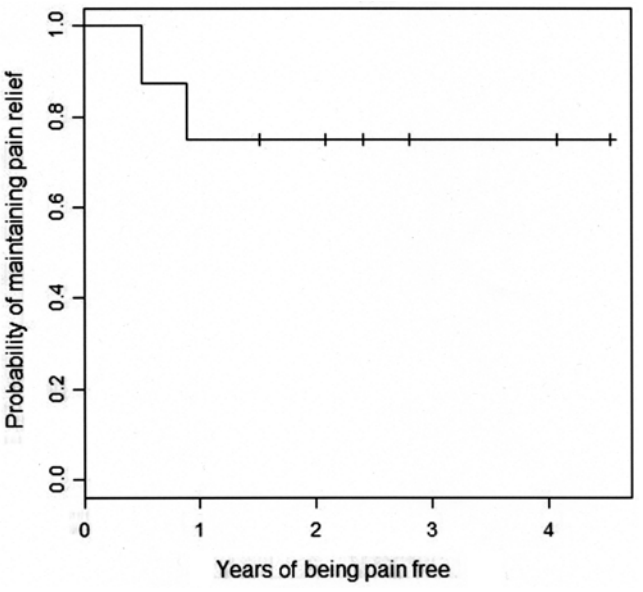

Fig. 4. Kaplan-Meier curve showing the actuarial rate for maintaining pain-relief rates after second GKS in the Marseille study.

Systematic Review

Reports Included. The combination of words "repeat AND radiosurgery AND trigeminal" in PubMed database gave a number of 25 papers, from which 10 were selected,[5,14,17,22,24,29,32,40,42,67] including 1 case report;[29] using "recurrent AND radiosurgery AND trigeminal" returned 48 studies, from which 7 were selected;[1,25–27,43,54,63] and using "salvage" AND "radiosurgery" AND "trigeminal" returned 1 study[38] that did not report the outcomes of interest, only the range of doses used at retreatment, so we excluded it. After a detailed research of references in the included studies and after analyzing all trials published on idiopathic TN treated with GKS, 3 further studies were included, giving a total of 20 studies (Tables 3–5).

Interestingly, no dedicated study was found when searching for retreatment using linear accelerators, only sparse information without outcomes.[13,57]

Study Analysis. The final analysis included 20 peer-reviewed papers treating the subject of repeat GKS for TN, for a total of 626 patients. Only 4 studies contained more than 40 patients. All reports were retrospective and only 4 had long-term follow-up.[17,32,40,62] Although this is a large number of patients, analysis was difficult because of study heterogeneity. First, the populations of patients were heterogeneous at baseline, in terms of previous surgeries (highly variable numbers and types) and inclusion of atypical cases and multiple sclerosis,[1,32,63] which are reputed to have a different initial pain cessation outcomes.[58] Second, there was no uniformity of patient selection criteria for retreatment. Third, outcomes were assessed differently; quality of life issues were reported sporadically[24] and, if so, on

TABLE 2: Assessment after second GKS in the Marseille study

Variable	No. of Patients (%)
initially pain free	8 (88.9)
post-GKS sensory dysfunction	3 (33.3)
mild	3 (33.3)
severe	0 (0)
BNI facial hypesthesia scale (GKS related)	
I (no facial numbness)	6 (66.7)
II (mild facial numbness)	3 (33.3)
III (facial numbness, somewhat bothersome)	0 (0)
IV (facial numbness, very bothersome)	0 (0)
recurrence of pain	2 (22.2)
no. of additional treatments after 2nd GKS	2 (22.2)
1	1 (11.1)
2	0 (0)
≥3	1 (11.1)
balloon microcompression	2 (22.2)
MVD	1 (11.1)

TABLE 3: Systematic review of the literature: demographics of patients undergoing second GKS*

Authors & Year	No./Total Patients	Center	Follow-Up Period in Mos (range)	Age in Yrs (range)	Mean Interval Btwn 1st & 2nd GKS (mos)
present study	13/737	Marseille (France)	median 33.9 (15.9–96)	median 64.4 (53.7–83.1)	median 72 (12–125)
Park et al., 2012	119/503†	Pittsburgh, PA (US)	median 48 (6–187)	median 74 (34–96)	median 26 (4–146)
Aubuchon et al., 2011	37	Florida (US)	mean 45.6 (7.2–86.4)	NA	mean 15.6
Jones et al., 2011	1	Seattle, WA (US)	24	72	11
Kimball et al., 2010	45/379	Memphis, TN (US)	mean 42 (1–122)	mean 68 (30–87)	mean 33 (3–138)
Verheul et al., 2010	79/365	Tilburg (the Netherlands)	median 28 (3–85)	NA	NA
Dvorak et al., 2009	28	Boston, MA (US)	median 19.7 (1.7–48.9)	median 63	median 18.1 (9–55.4)
Gellner et al., 2008	22/93	Graz (Austria)	mean 64.5 (13–142)	mean 73.5	mean 18.8 (6–63)
Huang et al., 2008	20/89	Taiwan (China)	mean 60 (32–87)	mean 61.8 (34–83)	mean 8 (4.67)
Wang et al., 2008	34/322	X'ian (China)	mean 21.6 (7–41)	median 68 (42–87) at 1st GKS	mean 17.4 (8–34)
Huang et al., 2006	28/118	Taiwan (China)	median 43	median 63 (34–77)	median 8 (3–67)
Pollock et al., 2005	19	Rochester, MN (US)	median 24 (5–67)	median 68 (43–83)	median 16 (4–55)
Sheehan et al., 2005	14/151	Charlottesville, VA (US)	median 19 (after first)	median 68	NA
Urgosik et al., 2005	19/107	Prague (Czech Republic)	median 36 (12–72)	median 75 (45–91)	median 12.5 (3–60)
Zhang et al., 2005	40	New York (US)	mean 28 (6–51)	median 73 (40–90)	mean 17 (5–48)
Herman et al., 2004	18/112	Baltimore, MD (US)	median 24.5 (6–65)	median 62 (31–89)	median 8 (3–42)
Brisman, 2003	45/335	Columbia, SC (US)	mean 15	mean 70	mean 18 (42–68)
Hasegawa et al., 2002	27/387	Pittsburgh, PA (US)	median 20.4	mean 68.7	mean 22.3 (6–73)
Shetter et al., 2002	19/240	Phoenix, AZ (US)	median 13.5	NA	NA
Zheng et al., 2001	12/80	Tianjin (China)	mean 18	mean 67 (32–92)	NA
Pollock et al., 2000	10/100	Rochester, MN (US)	median 15	median 68 (48–83)	median 13 (4–27)

* NA = not applicable.
† The original study published in 2010 by Kondziolka et al. had 503 patients. The paper on retreatments (Park et al., 2012) does not state how many total patients they treated to that date.

different scales. Last but not least, the techniques employed were also highly variable: target placement and dose prescription play a crucial role in outcomes and should not be neglected in this type of analysis.

Outcomes were highly variable, with a median rate of initial pain cessation of 88% (range 60%–100%) after second GKS and a median hypesthesia rate of 33% (range 11%–80%).[1,5,14,17,22,24–27,29,32,40,42,43,53,54,61–63,67]

Patient Profiles. Patients may have different response profiles to a first stereotactic radiosurgery, and they are heterogeneously represented in the literature: recurrent pain after complete response,[14,22,40,61] reasonable pain control but significant medication-related side effects or partial response,[17,43,54] or no response at all.[5,24] Recurrent pain after complete response is a widely accepted indication for repeat radiosurgery; interventions for the others depend on the center's policy. At Timone University Hospital, the patient criterion for retreatment was initial pain cessation without medication, lasting for at least 1 year.

In the published studies, the median time between first and second radiosurgery was 17 months (range 3–146 months); in the Marseille study it was 72 months (range 12–125 months; Table 3).

Technical Nuances. Technical nuances play a major role in surgical outcomes, especially regarding 2 aspects: target placement and cumulative dose. Secondary issues not specifically related to retreatment are placing 1 versus 2 isocenters, plugging (which increases the length of the treated nerve, the so-called Flickinger effect), and how the nerve recovers after a first GKS.

Target Placement. With some exceptions,[40,63] most of the studies reported using the DREZ as a retreatment target, with more than 50% using the identical location the first and second time (Table 4). Some reports, such as that by Zhang et al.,[67] suggested that a longer mean distance between isocenters (2.86 vs 1.93 mm) was associated with better outcomes.

Cumulative Dose. In the studies cumulative dose was reported to range between 40 and 90 Gy at retreatment (Table 4). Cumulative dose as both a value and a cutoff for safety and efficacy remains to be defined. Its real value is not just adding the first and the second dose. Zhang et al.[67] stated that if the dose at first GKS is 75 Gy and the dose at the second GKS is 40 Gy, with zero as the distance between isocenters, the cumulative dose would be 102 and not 115 Gy (however, biological equivalent dose has not been taken into account in this evaluation). For the same doses, but with a distance of 3 mm between the shots, Hasegawa et al.[22] found that the cumulative dose drops to 95 Gy.

Regarding efficacy, Pollock et al.[42] discussed the issue of a cumulative dose of 163.1 Gy versus lower doses

TABLE 4: Systematic review of the literature: details of GKS among patients undergoing second GKS*

Authors & Year	Initial Dose in Gy (range)	2nd Dose in Gy (range)	Cumulative Dose in Gy (range)†	Initial Target	2nd Target
present study	median 85 (70–90)	median 90 (70–90)	range 140–180	retrogasserian	identical
Park et al., 2012	median 80 (60–90)	median 70 (50–90)	median 145 (120–170)	3–4 mm	50% overlap
Aubuchon et al., 2011	mean 87.3 (80–90)	mean 84.4 (60–90)	mean 171.7 (140–180)	50% BS/plex triangularis	distally, unless 1st target distally
Jones et al., 2011	84	54	178	50% BS	identical
Kimball et al., 2010	80	70	150	REZ (50%)	4–5 mm distally
Verheul et al., 2010	80	80	160	REZ	50% overlap
Dvorak et al., 2009	median 80 (80–85)	median 45 (40–50)	median 125 (120–130)	20% BS	2-mm difference
Gellner et al., 2008	mean 75.2 (65–85)	mean 74.3 (65–75)	149.5 (130–160)	REZ (20% BS)	REZ (20% BS)
Huang et al., 2008	mean 79 (60–90)	mean 52 (40–76)	mean 131 (100–166)	REZ (20–30%)	identical
Wang et al., 2008	mean 73.4 (60–80)	range 60–75	range 120–155	3–4 mm REZ	identical
Huang et al., 2006	mean 79.3 (70–90)	mean 52 (40–76)	mean 131.3 (110–166)	REZ (20% BS)	identical
Pollock et al., 2005	median 81.6 (76.1–97.9)	median 76.1 (65.3–97.9)	median 163.1 (152.2–174.0)	20% or lower w/ the BS	anterior
Sheehan et al., 2005	median 80	≤70	150	NA	NA
Urgosik et al., 2005	range 70–80	range 70–80	range 140–160 (mainly same dose)	20% BS	2–4 mm distal
Zhang et al., 2005	75	40	115	40% BS	identical
Herman et al., 2004	median 75 (70–80)	median 70 (65–75)	median 145 (140–155)	REZ (20%)	identical
Brisman, 2003	median 75	median 40	115	BS 40–50%	NA
Hasegawa et al., 2002	mean 75.6 (50–80)	mean 64.4 (50–80)	139.4 (125–155)	20% touched the BS	anterior to 1st w/ only 50% overlap
Shetter et al., 2002	mean 78.2 (35–80)	mean 46.6 (35–80)	124.8 (70–160)	BS 50%	identical
Zheng et al., 2001	mean 75.6 (70–90)	mean 74.2 (70–80)	149.8 (140–170)	REZ	identical
Pollock et al., 2000	median 70	median 90 (70–120)	160 (140–190)	REZ	identical

* BS = brainstem; REZ = root entry zone.

† As additive value.

(148.5 Gy in the Pittsburgh group,[22] 143.4 Gy in the Baltimore group,[24] and 135.7 Gy in the Phoenix group[54]) and stated that there was higher initial pain cessation at higher doses, as much as 75% compared with a range between 19% and 53% for the lower doses.

Dvorak et al.[14] proposed the concept of tailoring the dose to an individual patient. For debilitating pain they propose cumulative doses of more than 130 Gy and potentially more than 150 Gy and accepting a higher rate of side effects; for patients with reasonable pain control but medication side effects, doses less than 130 Gy seemed more appropriate, with a lower rate of side effects. Dvorak et al. mainly analyzed 7 peer-reviewed papers, accounting for 215 patients, and found an association between cumulative dose and pain control ($p = 0.04$) but also new dysfunction ($p = 0.08$); furthermore, the association between pain control and new dysfunction was strong ($p = 0.02$). They concluded that a dose of 130 Gy or more was more successful in terms of pain control but increased dysfunction.

Little et al.[38] stated that it "seems not to be necessary to decrease the doses in patients with prior trigeminal dysfunction" and also that there is more Level III evidence for ranges of doses between 40 and 70 Gy. Hasegawa et al.[22] compared combined high doses (140–160 Gy) versus lower doses (120–135 Gy) and concluded that there was no difference in recurrence rates but that there was increased hypesthesia with the higher doses (32% vs 4%). They advocated limiting the cumulative dose to 140 Gy. Herman et al.[24] discussed a cumulative dose of 145 Gy (75 Gy at first GKS and 70 Gy at second GKS), with decreased efficacy but also a low incidence of facial numbness. Hasegawa et al.[22] suggested that "the best dose would eliminate facial pain completely and preserve facial sensation." To date, there is no established cut-off for dose, and there was a tendency to decrease the dose at second GKS in most studies to avoid dysfunction.

Outcomes. Outcomes are summarized in Table 5 and are detailed below.

Initial Pain Cessation. With repeat radiosurgery, for greater than 50% relief of initial pain the median was 88% (range 60%–100%); for complete relief, the median was 58% (range 18.5%–90%). After initial radiosurgery the ranges were 78%–94% and 32%–81%, respectively. After both first and second GKS, most patients became pain free during the first 6 months; the pain cessation rates were fairly consistent with observations after the first GKS.

TABLE 5: Systematic review of the literature: results of second GKS

Authors & Year	Initially Pain-Free >50%	Excellent Pain-Free (BNI Class I & II)	Trigeminal Dysfunction	New Facial Numbness
present study	89%	89%	33%	33.3%
Park et al., 2012	87%	32%	18%	18%
Aubuchon et al., 2011	81%	46%	57%	38%
Jones et al., 2011	100%	NA	NA	NA
Kimball et al., 2010	91.30%	69.5%	47.8%	45.6%; 8.7% bothersome
Verheul et al., 2010	96%	70%	NA	24%
Dvorak et al., 2009	61%	29%	29%	11%
Gellner et al., 2008	100.00%	76.2%	73.7%	73.7, 5.3% BNI III
Huang et al., 2008	60%	NA	NA	35%, 2 w/ BNI III, 1 w/ BNI IV
Wang et al., 2008	85.4%	53%	NA	11.8%, 1 as somewhat bothersome
Huang et al., 2006	68%	43%	36%	36%, 10.7 somewhat bothersome, 4% masseter weakness
Pollock et al., 2005	95%	74%	58%, 16% BNI III & IV	16% BNI III & IV, 11% corneal numbness
Sheehan et al., 2005	NA	NA	36%	36%
Urgosik et al., 2005	89%	58%	33%	33%
Zhang et al., 2005	65%	27%	10% (mainly dysesthesias), 3% severe	10% (mainly dysesthesias), 3% severe
Herman et al., 2004	88%	45%	11%, 5.5% BNI III & IV	11%, 5.5% BNI III & IV
Brisman, 2003	62%	22%	4% severe dysesthesias	8.8% BNI III, 4.4% BNI IV
Shetter et al., 2002	88%	53%	42%	42%
Hasegawa et al., 2002	85.2%	18.5%	12.7%	12.7%
Zheng et al., 2001	91.7%	75%	11%	11%
Pollock et al., 2000	90%	90%	80%	80%

Positive predictive factors for pain cessation rates taken from the published studies are complete pain relief after initial GKS, longer periods of pain relief, reduced topographic distribution of pain after a prior GKS, new trigeminal deficits, increasing isocenter distance between second and first GKS,[67] and higher radiation dose.[26] Negative predictors are no pain relief after a prior GKS[24] and having undergone prior surgical procedure(s). No correlation was found for age, sex, side, additive doses, or interval between first and second GKS[5,27,32] (Table 6).

Hypesthesia. The median rate for new hypesthesia after repeat GKS was 33% (range 11%–80%), much higher than that reported for first GKS (6%–54%). The main problem might not even be hypesthesia per se with retreatment but such complications as bothersome hypesthesia (up to 16%),[17,42] corneal numbness (up to 11%),[1,42] dry eye (up to 10.9%),[32] taste changes (up to 8.7%),[32] jaw weakness (up to 4%),[32] and anesthesia dolorosa (which was difficult to quantify due to heterogeneity and lack of reporting).[1]

Positive predictive factors for new hypesthesia after second GKS, taken from the published studies, are good response to initial GKS (even at low doses), an additive dose greater than 115 Gy, isocenter placement (nearly identical location being reported by some studies as creating dysfunction), cumulative radiation dose to the lateral pons (cutoff of 44 Gy), and cumulative DREZ dose (cutoff of 84.3 Gy).[1] No correlation was found with regard to prior surgeries,[26] pretreatment sensory impairment, first and/or second dose or additive doses,[26] or the distance between isocenters (considered by other studies to be a positive predictor)[42] (Table 7).

Summarizing current literature, hypesthesia onset is suggested to be a predictor for better long-term outcome but is not mandatory for maintaining pain relief. Also, in some studies, the occurrence of hypesthesia reached rates comparable to those with radiofrequency lesioning and/or balloon microcompression. Retreatment is more injuring than a first GKS.

Maintaining Pain Relief. As with all other techniques for TN, a second GKS is not a definitive therapy. There are 2 important issues when discussing maintenance of pain relief after second GKS: one is the necessity of having long-term follow-up, as recurrences are more likely to occur 15–18 months after treatment; the second is that reported rates are fairly consistent or better compared with results of the first GKS (but there is shorter available follow-up compared with first treatment).

In the published studies, recurrences ranged between 5.3% and 32% in the short term (median 24 months). Among studies reporting long-term follow-up, rates for maintaining pain relief at 5 years varied between 44.2%[40] and 72.7%.[17] Additionally, in some studies, such as that by Verheul et al.,[62] the curves for first and second GKS are almost identical for this outcome.

TABLE 6: Systematic review of the literature: predictors of initial pain cessation after second GKS

positive predictors
initial complete pain relief after a prior GKS
longer periods of pain relief after 1st GKS
reduced distribution after 1st GKS
new trigeminal deficits
increasing distance btwn isocenters of 1st & 2nd radiation dose
negative predictors
no pain relief after a prior GKS
prior surgical procedure
no correlation
age
sex
side
interval btwn GKS procedures
dose rate at 2nd GKS
radiation dose

Positive predictive factors were partial recurrence after first GKS (partial better than complete), recurrence in a reduced topographic distribution, and additional sensory dysfunction after a first treatment.[32]

Discussion

Medically unresponsive TN can be treated by 3 methods: MVD, percutaneous techniques, and GKS. With the MVD technique, Barker et al.[2] reported up to 70% of patients remaining pain free at 10 years; for patients undergoing repeat MVD, 42% of cases had excellent results at 10 years. Depending on the study, MVD recurrence rates on long-term basis range between 15% and 35%.[2–4,7,8,10–12,18,28,30,52,55,56] For percutaneous techniques, such as thermocoagulation, some trials reported a 57.7% pain-free response after a first procedure and up to 94% at 5-year follow-up after a second procedure.[31] Facial numbness has been reported to occur in between 58% and 79% of patients.[9,65] Gybels and Sweet[19] reviewed 8 published studies on thermocoagulation, involving more than 600 procedures; corneal numbness ranged from 1% to 35% and anesthesia dolorosa, from 0.6% to 25%.

TABLE 7: Systematic review of the literature: predictors of hypesthesia onset

positive predictors
prior surgeries
good response to initial GKS (even if 2nd GKS performed at low doses)
reduced distribution after 1st GKS
an additive dose above 115 Gy
nearly identical isocenter locations & mean dysfunction
cumulative max radiation dose to lateral pons (cutoff 44 Gy)
no correlation
prior surgeries
pretreatment sensory impairment
1st &/or 2nd dose, additive dose
distance btwn isocenters
which isocenter closer to brainstem

Repeat radiosurgery emerged as an alternative to these 2 techniques, especially during the last 10 years. A number of clinical retrospective trials have shown that second GKS is a safe and effective procedure, with comparable or better initial pain cessation rates, despite a higher toxicity, which seems to be the tradeoff for maintaining pain relief.[1,5,14,17,22,24–27,32,38,42,63] Nevertheless, there is little consistent information to council patients on an individual basis, due to heterogeneity among papers regarding selection criteria and treatment parameters.

Among the 497 patients included in our study with initial pain cessation after the first GKS, 34.4% (157 of 456 with ≥ 1-year follow-up) experienced at least 1 recurrence; 112 of 157 required further treatment. Thirteen (1.8%) of the 737 patients were considered for a second GKS, a rate smaller than found in the published peer-reviewed papers, which ranged in from 7%[22] to 23.7%[26] (Table 3); this is explained by a different strategy of repeat GKS in our study.

Patient selection for retreatment is probably one of the most important issues. Why to retreat, when to retreat, and the patient profile are key conditions for therapeutic success. Our center uses strict selection criteria for second GKS, related to an initial and prolonged pain cessation without medication, in the absence of other surgical alternatives. This is suggested by the median time for retreatment in our study, 72 months (range 12–125 months), compared with 17 months (range 12–125 months) in the literature reviewed. Also, previous studies discussing first GKS showed improved outcomes with no atypical features,[39,44] no prior surgical treatment,[6,39,41] or no new trigeminal deficits.[6,44] When reporting outcomes, we believe that these types of cases should be clearly separated.

Additionally, individual patient sensitivity to irradiation might play a role. We might be selecting a subgroup of patients sensitive to radiation when treating only those responding well to the first GKS.

Another issue is related to doses. For GKS, a minimum dose of 70 Gy necessary for efficacy was established in 1996 by a multicenter trial.[34] As a maximum, in a baboon model Kondziolka et al.[33] suggested that necrosis occurred at 100 Gy. In this range, higher doses are related to better efficacy.[53,64] Thus, our policy is to deliver 90 Gy at 100% isodose, whenever the morphology of the cistern allows this dose prescription, while keeping doses to the brainstem low. This dose allows a low rate of toxicity, provided that we use the retrogasserian target (7–8 mm from the emergence).[48] We kept the same dose and the same target placement at first and second GKS.

The radiation target is important with respect to initial pain cessation and side effects. The heterogeneity regarding radiation target in published studies makes the "ideal" target difficult to establish.

Current literature is sparse, and there is a need for more follow-up and uniformity to establish state-of-the-

art safety and efficacy for GKS retreatment. Pain control and recurrence rates seem comparable with first GKS in the literature we reviewed, with higher hypesthesia rates at second GKS in almost all studies. When investigating safety and efficacy, particular attention should be paid to individual patient characteristics at baseline, as well as to technical nuances, mainly target placement and radiation dose; additionally, the number of patients and duration of follow-up are important criteria.

Besides the relatively small sample size, our study raises the question of surgical alternatives after failed GKS for TN. The rates of initial pain cessation and recurrence seem comparable to or even better than those for the first GKS, according to different studies, but the toxicity is much higher, both in our study and in the published data. However, because of the small number of patients in our study and limited available follow-up and heterogeneity of treatment philosophies in the reviewed studies, we do not have the answer to the 3 cardinal questions regarding repeat radiosurgery in recurrent TN: which patients to retreat, which target is optimal, and which dose is optimal. Reassessment of our database in 20 years' time may offer sufficient numbers to answer these questions.

Conclusions

Our study is small compared with our general cohort due to very strict selection criteria for retreatment, mainly related to an initial and prolonged pain cessation without medication, in the absence of other surgical alternatives. Our study is differentiated from the other published studies by the use of the same technical parameters as the first GKS and much longer delay between first and second GKS, with a median of 72 months (range 12–125 months) at our institution compared with 17 months (range 3–146 months) in the literature. Current available studies suggest that second GKS is safe and effective, with an important increase in hypesthesia rates. Our attitude, due to this higher toxicity, is to propose MVD as a first intention therapy for recurrent TN after first GKS and to reserve second GKS for cases with no other surgical alternative.

Disclosure

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Address correspondence to: Constantin Tuleasca, M.D., Lausanne University Hospital, Neurosurgery Service and Gamma Knife Center, Rue de Bugnon 44-46, BH-08, CH-1011 Lausanne, Switzerland. email: constantin.tuleasca@gmail.com.